

Penicillin Allergies

Penicillin Allergies – Guide for Clinicians

Prevalence of Penicillin Allergy:

Approximately 10% of the patient population will report an allergic reaction to a penicillin class antibiotic. Of those who report a history of penicillin allergy, up to 90% are able to tolerate penicillins when challenged (1-3).

The reasons for the discrepancy between reported and actual penicillin allergy may be due to:

- Waning of penicillin specific IgE antibodies over time. It has been reported that up to 80% of patients may lose their IgE-mediated sensitivity to penicillins after 10 years of the initial reaction.
- A cutaneous reaction that was initially thought to be an allergy, but was actually a result of the underlying viral or bacterial infection, or an interaction between the infectious agent and the antibiotic given at the time.
- A drug side effect mislabeled as an allergic reaction.

The rate of penicillin-induced anaphylaxis is rare and is reported to be less than 1% in the literature (2, 4).

Coombs and Gell Hypersensitivity Classification (5, 6):

Classification	Mediator	Onset	Onset (previously sensitized)	Possible Clinical Reactions	Use skin testing?
I – Immediate-type hypersensitivity	IgE antibodies	0 to 1 hr (up to 72 hrs)	0 to 1 hr	Anaphylaxis, urticaria, angioedema, wheezing, hypotension	Yes
II – Antibody-antigen binding	IgG or IgM antibodies	> 72 hrs (up to 14 days)	24 to 36 hr	Hemolytic anemia, neutropenia, thrombocytopenia	No
III – Soluble antigen-antibody complexes	Antigen-antibody complexes	> 72 hours (up to 14 days)	24 to 36 hr	Serum sickness, vasculitis, drug fever, glomerulonephritis	No
IV – Delayed-type hypersensitivity	T-cells	> 72 hours (up to 3-4 weeks)	48 to 96 hr	Contact dermatitis, morbilliform eruptions, Steven-Johnson / toxic epidermal necrolysis	No

Penicillin-Cephalosporin Cross-Sensitivity:

The rate of penicillin-cephalosporin cross-sensitivity is overestimated in the literature and is likely dependent on the presence of a shared side chain with the penicillin rather than the core beta-lactam ring of the drug's molecular structure (2,7). A higher risk of allergic reaction is expected with cephalosporins that share a similar side chain as a beta-lactam to which a patient is allergic (see cross-sensitivity chart below).

****Please refer to the “Algorithm for Management of Penicillin Allergy” to help determine if a patient can safely be given a penicillin or cephalosporin and if performing penicillin skin testing is appropriate****

Penicillin-Cephalosporin-Carbapenem Cross-Sensitivity Chart (8, 9):

		Amoxicillin	Ampicillin	Cloxacillin	Penicillin	Piperacillin	Cefadroxil	Cefazolin	Cephalexin	Cephalothin	Cefaclor	Cefprozil	Cefotetan	Cefoxitin	Cefuroxime	Cefixime	Cefotaxime	Ceftazidime	Ceftriaxone	Cefepime	Ertapenem	Imipenem	Meropenem	
Penicillins	Amoxicillin	X	X	X	X	X	X	X	X	X	X	X												
	Ampicillin	X	X	X	X	X	X	X	X	X	X	X												
	Cloxacillin	X	X	X	X	X								X										
	Penicillin	X	X	X	X	X				X				X										
	Piperacillin	X	X	X	X	X																		
1 st Generation Cephalosporin	Cefadroxil	X	X				X	X	X	X	X	X												
	Cefazolin	Cefazolin shares no side chain and is safe to use in patients with a penicillin allergy history																						
	Cephalexin	X	X				X		X	X	X	X												
	Cephalothin				X				X	X	X	X		X			X							
2 nd Generation Cephalosporin	Cefaclor	X	X				X	X	X	X	X	X												
	Cefprozil	X	X				X	X	X	X	X	X												
	Cefotetan												X											
	Cefoxitin				X				X					X										
	Cefuroxime													X	X									
3 rd Generation Cephalosporin	Cefixime															X								
	Cefotaxime								X								X		X	X				
	Ceftazidime																	X		X				
	Ceftriaxone																X		X	X				
4 th Generation Cephalosporin	Cefepime															X		X	X					
Carbapenems	Ertapenem																				X	X	X	X
	Imipenem																				X	X	X	X
	Meropenem																				X	X	X	X

X – Indicate antibiotics that have a similar side chain or structure and a higher risk for cross-sensitivity

Penicillin Allergy Assessment and Testing:

In a large study evaluating the incidence of penicillin hypersensitivity (IgE mediated), it was found that in patients with a valid history of penicillin allergy, 21% had a positive skin test, while in patients with a questionable or invalid history, 10% and 4% had a positive skin test, respectively (10). Skin testing with both penicilloyl-poly-lysine (major determinant) and penicillin G (minor determinant) can identify up to 95% of patients with positive reactions. In the case of a negative skin test, 98% of patients will tolerate penicillin without any serious reaction (11). Penicillin skin testing or a graded challenge should be considered based on the patient's allergy history.

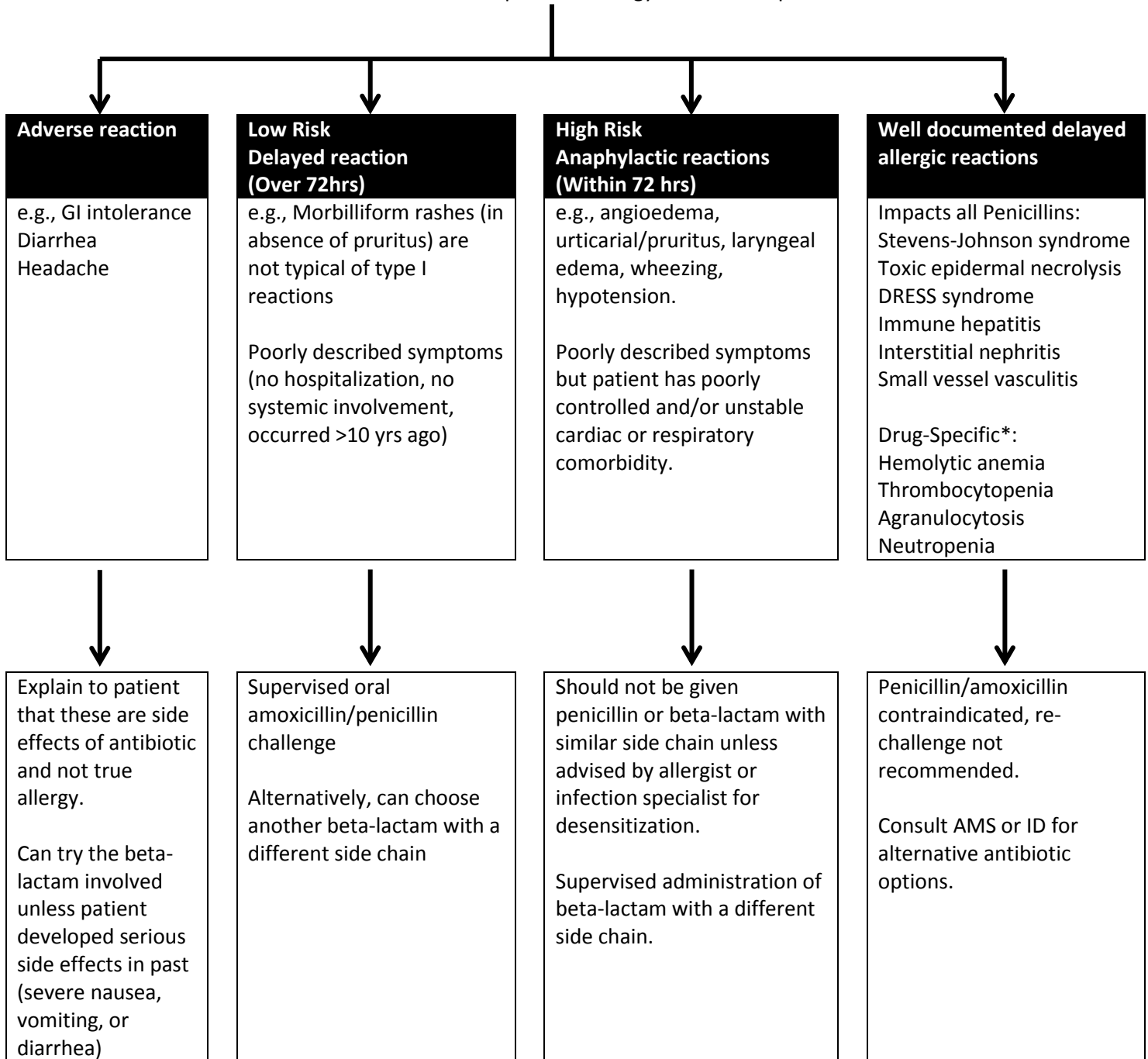
Despite the limitations of the available literature, the reported rate of allergic reaction with cephalosporins in a patient with a history of penicillin allergy is less than 1% (2). Furthermore, the rate of reaction to cephalosporin in patients with a positive penicillin skin test is approximately 2% (2). Therefore in patients with a history of non-severe penicillin reaction, the administration of a cephalosporin (that does not share a similar side chain as the culprit penicillin) can be safely given.

Penicillin Allergy Questionnaire

Rationale for Questionnaire	
<ul style="list-style-type: none"> Physicians are more likely to prescribe antimicrobials from other classes Patients with a beta-lactam allergy may be exposed to non-first line antibiotics Non-first line antibiotics may be less effective and more toxic increasing risk of undesirable outcomes (increased length of stay and <i>C. difficile</i> infections) Up to 90% of patients with a reported penicillin allergy can tolerate penicillin when challenged Questionnaire helps to identify patients that are deemed safe to undergo a penicillin challenge 	
Penicillin Allergy Questionnaire	
Skin Test	
1) Have you ever had a penicillin allergy skin test? <input type="checkbox"/> Yes <input type="checkbox"/> No	
Allergy Questions	
1) Can you describe the reaction? _____	
2) Was the reaction serious? <input type="checkbox"/> Yes <input type="checkbox"/> No	
3) Can you remember the allergic reaction yourself? <input type="checkbox"/> Yes <input type="checkbox"/> No	
a. If not, who informed you of it? _____	
4) How old were you at the time of reaction? _____	
5) How long after starting the antibiotic did the reaction begin? _____	
6) How was the reaction managed?	
a. Were you hospitalized? <input type="checkbox"/> Yes <input type="checkbox"/> No	
b. Was the medication discontinued? <input type="checkbox"/> Yes <input type="checkbox"/> No	
c. What happened after stopping the medication? _____	
7) Which antibiotic was prescribed to you? _____	
a. Do you remember why it was prescribed? _____	
8) Have you taken the antibiotic since? <input type="checkbox"/> Yes <input type="checkbox"/> No	
a. If yes, what was the outcome? _____	
9) Have you experienced this same reaction without taking the antibiotic? <input type="checkbox"/> Yes <input type="checkbox"/> No	
Assessment	
<input type="checkbox"/> Adverse Reaction	<ul style="list-style-type: none"> GI intolerance, diarrhea, headache
<input type="checkbox"/> Low Risk Delayed Reaction (“Benign” rash)	<ul style="list-style-type: none"> “Benign” rash only (e.g. Morbilliform rashes in the absence of pruritus) Poorly described symptoms (no hospitalization, no systemic involvement, occurred >10 years ago)
<input type="checkbox"/> High Risk Anaphylactic Reaction	<ul style="list-style-type: none"> e.g. Angioedema, urticaria/pruritus, laryngeal edema, bronchospasm, wheezing and hypotension
<input type="checkbox"/> Well Documented Delayed Reaction	<ul style="list-style-type: none"> Steven Johnson syndrome, toxic epidermal necrolysis, DRESS (drug reaction with eosinophilia and systemic symptoms), immune hepatitis, hemolytic anemia, thrombocytopenia, agranulocytosis, neutropenia, interstitial nephritis, small vessel vasculitis

Algorithm for Management of Penicillin Allergy

Risk stratification based on penicillin allergy assessment questionnaire



*Drug-induced hemolytic anemia, thrombocytopenia, agranulocytosis, and neutropenia are **drug-specific**. Cross-reactivity between cephalosporins and penicillins does not appear to occur. Avoid the offending drug.

Procedure for Amoxicillin/Penicillin Challenge

- 1) Obtain consent from patient for oral challenge.
- 2) Give 1/10th dose of the intended antibiotic or a single dose oral challenge of amoxicillin 500mg x 1 (supervised by RN).
- 3) Observe patients for at least 60 minutes for any immediate hypersensitivity reaction. Check vital signs at baseline and every 30 minutes x 2 after the first dose.

If patient develops anaphylaxis (see definition below):

- **Give EPINEPHrine 0.3mg IM x 1. May repeat in 5 minutes**
 - **Give diphenhydrAMINE 50mg IV/PO x 1**
 - **Notify MRP immediately.**
- 4) Follow up oral challenge and document outcome of oral challenge in chart. If no reaction observed, proceed with full treatment dose.
 - 5) If no reaction observed, document in EMR (under allergies) that patient tolerated oral challenge of antibiotic.
 - 6) If no reaction observed and allergy is documented on Pharmanet profile, de-label the allergy using the “Request to Inactivate Adverse Reaction/Clinical Condition” form.
 - 7) Monitor patient throughout stay for any delayed hypersensitivity.

Anaphylaxis is likely when any **one** of the following criteria is fulfilled:

- 1) Acute onset of an illness involving skin, mucosal tissue, or both (generalized hives, pruritis or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING:**
 - a. Respiratory compromise (dyspnea, wheeze-bronchospasm, stridor, hypoxemia)
 - b. Reduced BP or associated symptoms (hypotonia, collapse, syncope, incontinence)
- 2) TWO OR MORE OF THE FOLLOWING that occur rapidly *after exposure to a likely allergen for that patient* (minutes to several hours)**
 - a. Involvement of the skin mucosal tissue (e.g. generalized hives, itch-flush, swollen lips-tongue-uvula)
 - b. Respiratory compromise (dyspnea, wheeze-bronchospasm, stridor, hypoxemia)
 - c. Reduced BP or associated symptoms (hypotonia, collapse, syncope, incontinence)
 - d. Persistent gastrointestinal symptoms (crampy abdominal pain, vomiting)
- 3) Reduced BP *after exposure to a KNOWN allergen for that patient* (minutes to several hours)**
 - a. Systolic BP <90mmHg or >30% decrease from baseline